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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,594	11/14/2003	Mohamed Attawia	3518.1012-005	3230

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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1649	

MAIL DATE	DELIVERY MODE
05/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,594	ATTAWIA ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,11-17,20-24 and 31-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,11-17,20-24 and 31-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment filed 6/27/08 has been entered.

2. Applicant's arguments filed 6/27/08 have been fully considered but they are not deemed to be fully persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims **1-3, 6, 11-16, 20-24, 31 & 33** stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al (2003; IDS Ref #AU), for the reasons made of record in Paper No: 20071211, and as follows.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 10/631,487, etc. fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application, for the reasons previously made of record, and as follows.

In particular, '487 describes administering high affinity anti-MMP compounds (HAAMMP) to treat degenerative intervertebral disc disease. Administering HAAMMP with "additional therapeutic agents", such as "viable cells" (e.g., col. 11) is also contemplated. In contrast, no broader scope of administering solely "autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc" is described. Nor are all current claim limitations contemplated; thereby, failing to meet the requirements under 35 U.S.C. 112, first paragraph for the instantly claimed invention. Therefore, priority is granted only to the filing date of 10/714,559 (i.e., 11/13/2003).

The Attawia Declaration under 37 CFR 1.132 filed 6/27/08 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. 103 over Sakai et al (9/2003); or Sakai et al. in view of El-Khoury et al (1991), or Sakai et al. in view of El-Khoury et al. and further in view of McMillan et al (2002); or Sakai et al. in view of Tanney et al (1980), or Sakai et al. in view of Russell et al (5/2003); or Sakai et al. in view of Russell et al. and further in view of El-Khoury et al, as set forth in the last Office action because:

This is a rejection under 35 U.S.C. 103, and not 35 U.S.C. 102. In other words, although Declarant is correct that Sakai et al. does not teach use of uncultured MSC (cells) to treat a degenerative intervertebral disc, different motivations (e.g., as actually made by the Examiner in the pending rejections) are not required to be the same as those presented, or putatively presented, by Sakai; especially when Declarant's opinion on what Sakai et al may have also thought, or not, is not supportable. Accordingly, any supposition by Declarant that if Sakai "contemplated [or not] that administering uncultured cells is an obvious improvement over the[ir] methods", they would have used such as "a control to show the benefits of uncultured

cells in therapy" is simply unsupportable, and more importantly, not on point with the actual rejections of record. Nor are any teachings of Caplan et al. or Haynesworth et al. part of the instant rejections (e.g, as it relates to *pp* #s 15-17). In fact, Declarant's comments that "it was well known in the field that *ex vivo* cell culture is highly susceptible to various types of contamination" actually supports the obvious rejections of record, that is was obvious to substitute use of uncultured MSCs for cultured MSCs because of the improved clinical efficacy in treating intervertebral disc disease quicker (i.e., within hours, instead of days later) and by using fresher, potentially more viable autologous cells, which do not require a marker (i.e., Ad-lacZ), which also requires culturing, to demonstrate MSC survival. Finally, Declarant's reliance on a reference published 5 years after the priority of the instant application as basis to what he thinks should have been obvious to "scientists of ordinary skill in the art of regenerative medicine" is also not persuasive, because obviousness is determined as of the filing date of the instant application, and because what Declarant's opinion on what is putatively obvious, or not, 5 years after-the-fact is immaterial to what the actual rejections state; especially in light of the holdings of the court in KSR, as will be further discussed below. Thus Declarant's opinions are not found persuasive.

Applicants argue on pages 2-6 of the response that "Sakai *et al.* do not teach or suggest administering uncultured mesenchymal stem cells (MSCs)", that "Sakai *et al.*, in fact, had another motivation to culture and purify the MCSs" and refers to the Attawia Declaration, that "the authors' emphasis on the importance of using an Atelocollagen gel matrix as a carrier in their experiment… [which putatively] teaches away from use of uncultured cells in Applicants' claimed method", that "administering uncultured mesenchymal stem cells would not have been

obvious to a person having ordinary skill in the art… because there was a low expectation of success", that "40,0000 mesenchyma stem cells purified and embedded in Sakai et al's Atelocollagen gel… is still likely a mush higher number that if Sakai et al. skipped the culture step", and discuss the teaches of Centeno et al (2008) in the Attawia Declaration (which was published 5 years after the priority date of the instant application), while further arguing unsupported assertions about what constitutes "motivation to optimize administration volume…".

In contrast to Applicants' assertions, the issue remains that MPEP 2145 makes clear that motivation to combine references [or motivation using a single reference] does not need to be the same as Applicants', or Declarant's, and that alternatively arguing differences, or "special" advantages of their invention do "not render nonobvious an otherwise known invention". As previously made of record, the previous Examiner stated that Sakai needed to label his cells "to confirm that had survived in vivo", and it is well known in the art that only proliferating cells are amenable to infection with a adeno-lacZ marker virus. Therefore, any assertion (e.g., as argued on page 3 of the response) on what Sakai's intensions truly were, or were not, simply is mere speculation. The Examiner's position remains that no requirement for culturing reasonably existed based on a fair reading of Sakai et al., nor does Sakai reasonably "teach away" from Applicants' claimed invention, in contrast to Applicants'/Declarant's assertions.

In summary, Sakai et al specifically teach "autologous MSCs embedded in Atelocollagen gel were transplantated into discs [having a nucleus pulpsus] of rabbits which had undergone a procedure proven to induce degeneration [of the intervertebral disc]", and that "Atelocollagen gel served as an important carrier of MSCs, *permitting proliferation, matrix synthesis and*

differentation of MSCs [after transplantation] [emphasis added]" (see Abstract). In contrast, prevention of "proliferation , matrix synthesis and differentiation" after transplantation of the MSCs in the Atelocollagen gel is not claimed. Nevertheless, this is not a rejection under 35 U.S.C. 102, but a rejection under 35 U.S.C. 103. So whether Sakai et al happens to require culturing their MSCs before tranfection with a AD-lacZ marker can occur, in order to confirm whether their cells survive their particular experimental procedure, this culturing step does not negate, or reasonably "teach away" from any other teachings of Sakai et al. that are *prima facie* obvious to one of ordinary skill in the art. *In arguendo*, the motivation to combine or substitute can arise from the expectation that the prior art elements (i.e., cultured or uncultured MSCs) will perform their expected functions to achieve their expected results (i.e., treat degenerative disc disease) when combined or substituted for their common known purpose. See MPEP 2144.07

Accordingly, consistent with that held by the Supreme Court in KSR International Co. v. Teleflex Inc. et al (82 USPQ2d 1385 (2007)), in which the simple substitution of one known, equivalent element [i.e., culturing versus unculturing the same MSCs cells] for another to obtain predictable results [i.e., treating a degenerated intervertebral disc], or the combining of prior art elements [i.e., culturing versus nonculturing cells] according to known methods [of eventually proliferating the same MSCs cells *in vivo* in a transplanted matrix] to yield predictable results [i.e., treatment of the degenerative disc disease], reasonably supports a *prima facie* case of obviousness, especially given a finite number of predictable solutions [i.e., culturing or not culturing MSCs cells before addition of matrix gel for subsequent implantation] where it would be obvious to try based on the state of the art at the time of filing Applicants' invention (i.e., 2003).

5. Claims 1-3, 6, (7-in body of the rejection), 11-16, **20-24**, 31 & 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al (2003; IDS Ref #AU), as applied to claims **1-3, 6, 11-16, 20-24, 31 & 33** above, and further in view of El-Khoury et al (1991), for the reasons made of record in Paper No: 20071211, and as follows.

Applicants reiterate similar arguments as previously addressed or addressed above, which therefore, are not persuasive for the reasons made of record.

In response to Applicant's other arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

6. Claims 1-3, 6, 11-14, **15**, 16, **20-24**, 31, **33** & 34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al (2003; IDS Ref #AU), as applied to claims **1-3, 6, 11-16, 20-24, 31 & 33** above, and further in view of McMillan et al (2002), for the reasons made of record in Paper No: 20071211, and as follows.

Applicants reiterate similar arguments as previously addressed or addressed above, which therefore, are not persuasive for the reasons made of record.

In response to Applicant's other arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary

reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Consistent with that held by the Supreme Court in KSR International Co. v. Teleflex Inc. et al (82 USPQ2d 1385 (2007)), in which the simple substitution of one known, equivalent element [i.e., an intraoperative procedure to transplant/transfuse autologous RBCs] for another to obtain predictable results [i.e., intraoperative procedure to transplant autologous MSCs], or the combining of prior art elements [i.e., culturing versus nonculturing cells] according to known methods [of eventually proliferating the same MSCs cells *in vivo* in a transplanted matrix] to yield predictable results [i.e., treatment of the degenerative disc disease], reasonably supports a *prima facie* case of obviousness, especially given a finite number of predictable solutions [i.e., culturing or not culturing MSCs cells before addition of matrix gel for subsequent implantation, and use of uncultured autologous MSCs] where it would be obvious to try based on the state of the art at the time of filing Applicants' invention (i.e., 2003).

7. Claims 1-4, 6, 11-16, 20-24, 31 & 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al (2003; IDS Ref #AU), as applied to claims **1-3, 6, 11-16, 20-24, 31 & 33** above, and further in view of Tanney et al (1980), for the reasons made of record in Paper No: 20071211, and as follows.

Applicants reiterate similar arguments previously addressed or addressed above, which therefore, are not persuasive for the reasons made of record.

In response to Applicant's other arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Consistent with that held by the Supreme Court in KSR International Co. v. Teleflex Inc. et al (82 USPQ2d 1385 (2007)), in which the simple substitution of one known, equivalent element [i.e., concentrating bacterial cells by filtration] for another to obtain predictable results [i.e., concentrating MSC (cells) by filtration], or the combining of prior art elements [i.e., culturing versus nonculturing cells] according to known methods [of eventually proliferating the same MSCs cells *in vivo* in a transplanted matrix] to yield predictable results [i.e., treatment of the degenerative disc disease], reasonably supports a *prima facie* case of obviousness, especially given a finite number of predictable solutions [i.e., culturing or not culturing MSCs cells before addition of matrix gel for subsequent implantation, and use of the same filtering method for concentrating cells] where it would be obvious to try based on the state of the art at the time of filing Applicants' invention (i.e., 2003).

8. Claims 1-3, 6-7, 11-16, 20-24, 31-32 & **33** stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al (2003; IDS Ref #AU), as applied to claims **1-3, 6, 11-16, 20-24, 31 & 33** above, and further in view of Russell et al (5/2003), for the reasons made of record in Paper No: 20071211, and as follows.

Applicants reiterate similar arguments previously addressed or addressed above, which therefore, are not persuasive for the reasons made of record.

In response to Applicant's other arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

9. Claims 1-3, 6, **7**, 11-16, **20-24,** 31, **32** & 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sakai et al (2003; IDS Ref #AU), as applied to claims **1-3, 6, 11-16, 20-24, 31 & 33** above, in view of Russell et al (2003), as also applied to claims **7 & 32** in pp #8**,** and further in view of El-Khoury et al (1991), for the reasons made of record in Paper No: 20071211, and as follows.

Applicants reiterate similar arguments previously addressed or addressed above, which therefore, are not persuasive for the reasons made of record.

In response to Applicant's other arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Stucker, can be reached on (571) 272-0911. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Robert C. Hayes/
Primary Examiner, Art Unit 1649
April 30, 2009